Publications

Clinics of Oncology

Case Presentation

Systemic Therapy Combined with Prostate-Directed Therapy for Oligometastatic Prostate Cancer with Neuroendocrine Differentiation: A Case Report

Zhou F[1], LIU J[1], Renn S[1], Wang D[1*]

[1]Department of Invasive Surgery, Sichuan Academy of Medical Sciences & Sichuan Provincial People's Hospital Sichuan, China

Volume 1 Issue 3- 2018
Received Date: 20 June 2018
Accepted Date: 10 July 2018
Published Date: 18 July 2018

2. Keywords

Prostate cancer; Neuroendocrine differentiation; Oligometastasis; Androgen deprivation therapy Radical prostatectomy; Combinatorial immunotherapy

1. Abstract

We report a case of a 63-years-old man who presented with oligometastatic prostate cancer of pT2N0M1b, Gleason score 5+4 prostatic adenocarcinoma, with neuroendocrine differentiation. The patient underwent systemic therapy (androgen deprivation therapy, ADT) combined with prostate-directed therapy (Radical Prostatectomy, RP) with subsequent reduction of serum PSA to very low levels. The patient is currently on Radiotherapy (RT). This is a rare case of Prostate Cancer (PCa) with oligometastasis.

3. Background

Prostate cancer is a very common form of cancer worldwide, with millions of new cases every year, accounting for 1/4 of all cancer cases in men, and is the second most common cause of cancer-related mortality among men [1,2]. The overwhelming majority of Prostate Cancers (PCa) are adenocarcinomas most of which are low-risk cases with excellent long-term survival rates. In contrast, neuroendocrine differentiated prostate adenocarcinoma is rare and has poor overall survival [3]. We report a case, of a man who presented with oligometastases of T2N0M1b, Gleason score 5+4 PCa, with Neuroendocrine Differentiation (NED).

4. Case Presentation

In 2017, a 63-year old male came to our observation with one year history of dysuria and pain on right hip. On digital rectal examination, prostate was fairly enlarged. The prostate specific antigen (PSA) level (2017-09) was 116.98 ng/ml. Prostate Magnetic Resonance Imaging (MRI) (2017-09) **(Figure 1)**:

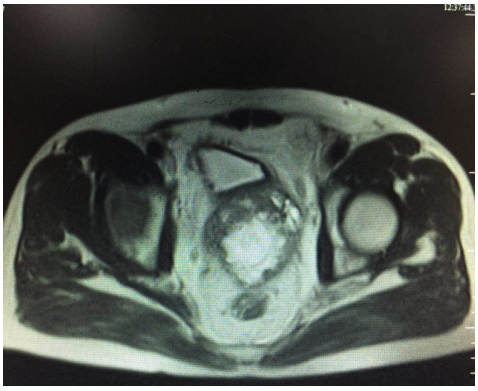

Figure 1: Prostate MRI showing prostate enlarged measuring about 6.6X6.8X9.6cm, slightly longer T1 signal shadow, see flaky liquefaction zone, enhanced scan solid region unevenly enhanced, partial capsule is not complete, consider the probability of prostate Ca, the rectum not invaded, no evidence of pelvic lymphadenopathy was found.

Prostate enlarged measuring about 6.6X6.8X9.6cm, slightly longer T1 signal shadow, see flaky liquefaction zone, enhanced scan solid region unevenly enhanced, partial capsule is not complete, consider the probability of prostate Ca, the rectum not invaded, no evidence of pelvic lymphadenopathy was found. Whole body bone imaging (2017-09) **(Figure 2)**:

***Corresponding Author (s):** Dong Wang, Department of Invasive Surgery, Sichuan Academy of Medical Sciences & Sichuan Provincial People's Hospital Sichuan, China, E-mail: wangdong_robot@163.com*

Citation: Zhou F, LIU J, Renn S, Wang D, Systemic Therapy Combined with Prostate-Directed Therapy for Oligometastatic Prostate Cancer with Neuroendocrine Differentiation: A Case Report. . Clinics of Oncology. 2018; 1(3): 1-4.

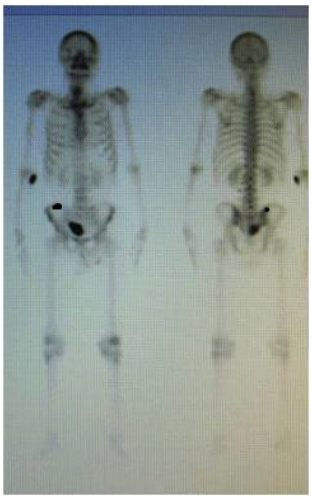

Figure 2: Whole body bone imaging showing irregular form of aggregation of radioactivity on right iliac bone: Bone neoplastic lesions, tumor bone metastasis.

Irregular form of aggregation of radioactivity on right iliac bone: Bone neoplastic lesions, Tumor bone metastasis. Prostate puncture biopsy: prostatic adenocarcinoma, with NED, with Gleason's score of 5 + 4 = 9. Immunohistochemically, the tumor cells were CK (+) ; PSA (+) ; P504S (+) ; CD (+) ; Syn (-) ; CgA (-) ; P63 (-) ; GATA3 (-) ; Hi-ck (-) ; AR (+) ; ki-67 (30%) . clinical TNM classification: T3aN0M1b

5. Treatment

The recommendation of androgen deprivation therapy (ADT) with Triptorelin 3.75mg per month and Zoledronic acid 4mg per month was given, which the patient agreed to. 4 weeks later, serum PSA sharply declined (10.196 ng/ml), dysuria and pain relieved. After 6 months treatment, Serum PSA declined to 0.168 ng/ml **(Figure 3)**. Prostate MRI: The size of the prostate gland was reduced, and no swelled lymph nodes were seen in the pelvic cavity. Whole body bone imaging: no new bone metastases could be found.

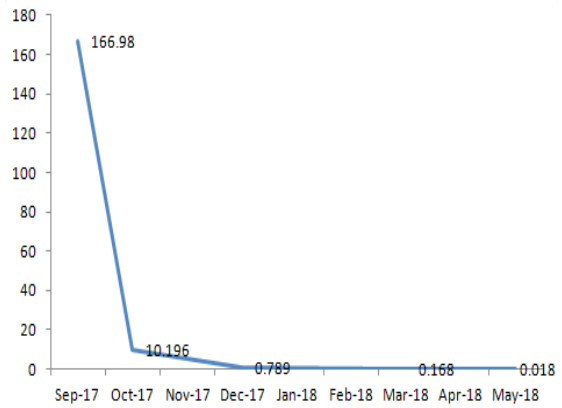

Figure 3: The PSA level was 116.98 ng/ml before treatment. After 4 weeks ADT treatment, serum PSA sharply declined (10.196 ng/ml), dysuria and pain relieved. After RP treatment, Serum PSA declined to 0.018 ng/ml.

The patient underwent robot-assisted laparoscopic Radical Prostatectomy (RP) with Pelvic lymph Node Dissection (PLND), with continuation of the ADT and zoledronic acid treatment. Postoperative pathological diagnosis: prostatic adenocarcinoma, with NED, with Gleason's score of 5 + 4 = 9. Margin (-) ; seminal vesicle (-) ; regional lymph node (0/6): right closed-cell lymph node(-), Left-handed obturator lymph node (-), left external iliac lymp h node (-), right external iliac lymph node (-) , left internal iliac lymph node (-), right internal iliac lymph node (-). Postoperative pathological stage: pT2N0M1b. One month after the surgery urinary continence was good, PSA: 0.018ng/ml.

The patient is currently on radiotherapy (External-Beamradiationtherapy, EBRT).

6. Discussion

According to the American Society of Clinical Oncology, National Comprehensive Cancer Network for Prostate cancer, and the Cancer Care Ontario clinical practice guideline, the main option for patients with metastatic PCa is systemic Androgen Deprivation Therapy (ADT), with bone antiresorptive therapy with denosumab or zoledronic acid if bone metastases present, which is however supported by strong evidence [4,5]. At least 90% of prostate cancers are initially diagnosed as acinar adenocarcinomas [6], which are almost always androgen dependent [3]. After 6 months treatment, serum PSA sharply declined, dysuria and pain relieved, the size of the prostate was reduced, and no evidence of new bone metastases was found.

During the treatment, we considered that what we can do more. Hellman proposed the concept of "Oligometastases". A state between the tumor confined to the primary lesion and extensive distant metastasis. The number of metastases is limited and the organ of transfer is specific: metastatic lesions confined to lymph nodes or bones (non-visceral metastases), and fewer than 5 metastatic lesions. At this stage, local directed treatment may be better effects [7,8].

Previous idea that locally advanced prostate cancer (T3) could not be cured by surgery, however, there are studies show that patients with advanced prostate cancer received RP may have survival benefit compared with patients with ADT only [9]. Comen et al. [10] believed that removing primary part of metastatic tumor reduce growth factor and immunosuppressive cytokines which could be the reasons for the benefits of prostate cancer patients. Leyh-Bannurah SR pointed out that the treatment of primary prostate lesions in metastatic prostate cancer can improve patient survival. In metastatic prostate cancer (mPCa), Local Therapy (LT) results in lower mortality relative to No Local Therapy (NLT). Within LT, lower mortality is recorded after RP than

Copyright ©2018 Wang D. This is an open access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and build upon your work non-commercially.

Radiation Therapy (RT), which mean that individuals with prostate cancer that spreads outside of the prostate might still benefit from prostate-directed treatments, such as radiation or surgery, in addition to receiving androgen deprivation therapy [11].

So, after 6 months treatment, when PSA declined and size of the prostate was reduced, the patient underwent robot-assisted laparoscopic RP with PLND, with continuation of the ADT and zoledronic acid treatment, and EBRT for bone metastases.

However, after an initial period of disease control through targeting the androgen axis, the disease almost inevitably progresses to castration-resistant prostate cancer (CRPC) [12]. A neuroendocrine pattern is frequently observed in the cellular composition of CRPC, which was not present in the initial diagnosis [13]. The emergence of this Neuroendocrine (NE) pattern in CRPC has been attributed to the effect of androgen deprivation therapy and two main mechanisms have been hypothesized. The first hypothesis suggests that, under prolonged hormonal manipulation, the resistant neuroendocrine, like tumor cell populations are selected from an initially heterogeneous tumor. The second hypothesis suggests that prolonged androgen deprivation may activate a process referred to as neuroendocrine transdifferentiation, which enables prostatic adenocarcinoma cells to acquire neuroendocrine characteristics [3,12,14]. Neuroendocrine tumorigenesis does not result from the proliferation of prostate NE cells. Rather, this carcinoma arises from the differentiation of prostate adenocarcinoma into "NE-like" cells [3]. These cells do not express androgen receptors or PSA, elucidating why NE PCa is not responsive to aggressive Androgen Deprivation Therapy (ADT) and is not associated with an elevated PSA. In addition, several series have suggested that ADT, the standard treatment in men with advanced PCa, may induce NED [15]. Fortunately, Androgen Deprivation Therapy (ADT) still works, which means that it is still Metastatic Hormone-Sensitive Prostate Cancer (mHSPC). Nicolas Mottet et al. [16] pointed out that early treatment with abiraterone plus ADT could prolong overall survival compared to ADT alone for patients with mHSPC, but no significant survival benefit for patients with Hormone-Sensitive Prostate Cancer (HSPC), which should help set the minimum the new Standard Of Care (SOC) based on the best available evidence and for the benefit of the majority of patients. For men presenting with mHSPC and starting ADT, Abiraterone + Prednisone must be regarded as another standard therapy abreast docetaxel.

Combinatorial immunotherapy may be a new way for CRPC. A clinical pathway hypothesis of Immunologic Checkpoint Block (ICB) combined with Myeloid Derived Suppressor Cells (MDSCs) targeted therapy for mCRPC is a new idea. Immune checkpoints are paired receptor-ligand molecules with interactions that suppress immune responses, the first to be found and identified as an immune checkpoint receptor, the cytotoxic T lymphocyte antigen 4 (CTLA-4), ICB produces a long lasting therapeutic response in important subsets of patients across multiple cancer types. However, mCRPC showed absolute resistance to ICB, but targeted therapy with agents that inhibit MDSC infiltration frequency and immunosuppressive activity can synergize with ICB to invigorate T cell immunity in the prostate tumor microenvironment thus impair CRPC progression, which gave us something new: inhibition of the activation of other inhibitory pathways after one immunologic checkpoint blocked may neutralize the anti-tumor effects, so the combination of two or more immune checkpoint inhibitors was expected to achieve better tumor inhibition [17].

7. Conclusion

It was the rare presentation of a oligometastatic PCa with NED in adult patient who underwent ADT, RP and RT. PCa with NED will turn to CRPC soon, even it is still hormone-sensitive after 6 month ADT treatment. Combinatorial immunotherapy may be a new idea for CRPC.

The dose distributions of this first cohort of patients are favorable for both target coverage and organs at risk dose limits and seem indicate that SBRT-VMAT planning in conjunction with MRI-based prostate is safe for localized prostate cancer patients at low/intermediate risk.

Our moderate acute toxicity data are consistent with the robustness of the planned dose distributions.

Finally, despite these encouraging results, longer follow up periods are desirable to confirm them.

References

1. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer. 2015;136:E359-86.

2. Siegel RL, Miller KD, Jemal A. Cancer statistics. CA Cancer J Clin. 2015;65:5-29.

3. Terry S, Beltran H. The many faces of neuroendocrine differentiation in prostate cancer progression. Front Oncol. 2014;4:60.

4. Basch E, Loblaw DA, Oliver TK, Carducci M, Chen RC, Frame JN, et al. Systemic therapy in men with metastatic castration-resistant prostate cancer: American Society of Clinical Oncology and Cancer Care Ontario clinical practice guideline. J Clin Oncol. 2014;32:3436-48.

5. Carroll PH, Mohler JL. NCCN Guidelines Updates: Prostate Cancer and Prostate Cancer Early Detection. J Natl Compr Canc Netw. 2018;16(5S):620-3.

6. Humphrey PA. Histological variants of prostatic carcinoma and their significance. Histopathology. 2012;60(1):59-74.

7. Weichselbaum RR, Hellman S. Oligometastases revisited. Nat Rev Clin Oncol. 2011;8(6):378-82.

8. Weichselbaum RR, Hellman S. Oligometastases. J Clin Oncol, 1995;13(1):8-10.

9. Ward JF, Slezak JM, Blute ML, Bergstralh EJ, Zincke H. Radical prostatectomy for clinically advanced (cT3) prostate cancer since the advent of prostate-specific antigen testing: 15-year outcome. BJU Int. 2005;95(6):751-6.

10. Comen E1, Norton L, Massagué J. Clinical implications of cancer self-seeding. Nat Rev Clin Oncol. 2011;8(6):369-77.

11. Leyh-Bannurah SR et al. Local Therapy Improves Survival in Metastatic Prostate Cancer. Eur Urol. 2017;72(1):118-24.

12. Nouri M, Ratther E, Stylianou N, Nelson CC, Hollier BG, Williams ED. Androgen-targeted therapy-induced epithelial mesenchymal plasticity and neuroendocrine transdifferentiation in prostate cancer: An opportunity for intervention. Front Oncol. 2014;4:370.

13. Matei DV, Renne G, Pimentel M, Sandri MT, Zorzino L, Botteri E, et al. Neuroendocrine differentiation in castration-resistant prostate cancer: A systematic diagnostic attempt. Clin Genitourin Cancer. 2012;10:164-73.

14. Beltran H, Tagawa ST, Park K, MacDonald T, Milowsky MI, Mosquera JM, et al. Challenges in recog-nizing treatment-related neuroendocrine prostate cancer. J Clin Oncol. 2012;30:E386-9.

15. Grigore AD, Ben-Jacob E, Farach-Carson MC. Prostate cancer and neuroendocrine differentiation: more neuronal, less endocrine? Front Oncol. 2015;5:37.

16. Nicolas Mottet, Maria De Santis, Erik Briers. Updated Guidelines for Metastatic Hormone-sensitive Prostate Cancer: Abiraterone Acetate Combined with Castration Is another Standard. European Urology. 2018;73(3)316-21.

17. Xin Lu, James W. Horner, et al. Effective Combinatorial Immunotherapy for Castration Resistant Prostate Cancer. Nature. 2017;543(7647):728-32.